WHICH CAME FIRST - THE BIOLOGICAL CELL OR THE CELL MEMBRANE?

Mel Rosenberg
Student number:
05533567
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INTRODUCTION

Membranes are a ubiquitous phenomenon in biological systems*(1). Every living cell has a surrounding plasma membrane which constitutes a separate phase (2). Eucaryotic cells, in addition, have intracellular membranes which surround many organelles and, in some cases, themselves constitute organelles (3).

The two major molecular components of biological membranes are invariably lipids and proteins. A great diversity exists, however, in the ratios of these components, in the minor constituents, and in the specific molecular composition (4). Each biological membrane is unique in composition and many have specific functions; on the other hand, many similarities, not only in gross chemical composition, but also in physical and chemical behaviour (5), molecular structure (as observed, for example in the electron microscope (6,7,8)), and basic biological properties (9). These similarities have prompted the construction of a wealth of general membrane models (10,11,12), and reviews thereon (13,14,15), which attempt to reconcile similar membrane characteristics in terms of a general molecular structure**.

Cell membranes are essential components of the contemprorary living cell. It is this barrier, only a few molecules in thickness, which sequesters the living, metabolizing cytoplasm from the external environment. When the membrane of an erythrocyte is disrupted, the cell matter spills out into the aqueous sur-

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* "All cells have confining membranes" (1).

** There also exists the opinion that the differences in the structures of biological membranes are irreconcilable in any one model, however general.

roundings (16). Even cells which are encompassed by thicker polymeric cell walls also lose their viability unless their cell membrane is intact. Compartmentation is only one of many varied and elegant functions which can be ascribed to membranes, yet clearly illustrates their vital role in the living process.

The evolution of the biological membrane as a function of the history of the development of life itself is a subject of speculative interest. Do the present similarities in biological membranes reflect a common precursor? If so, when did this original membrane develop? Alternatively, do the dissimilarities in membranes indicate that they evolved under different circumstances, and perhaps in different eras? In the latter case, the similarities can be ascribed to parallel results in the evolutionary search of the best system to fulfil similar functions. Were cells once extant without a separate phase boundary?

Which came first - the biological cell or the cell membrane?

Although any conclusions on this question would, of course, be impossible to verify, the teleological implications are worthy of consideration. Many scientists engaged in biological research tend to consider cell organelles in general, the membrane among them, in terms of their obvious, present functions*(17). If, indeed, the membrane evolved in cells already viable and functioning, perhaps the membrane can be thought of as an organelle whose structure arose in response to functional needs which still exist (therefore, so does the membrane). On the other hand, recent experiments, mostly in the research of artificial lipid membranes, lend credence to the theory first advanced by Goldacre (18), which postulates that mem-

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* Albert Lehninger, for example, writes in his acclaimed textbook: "...each component part of a living organism appears to have a specific purpose or function. This is true not only of intracellular structures, such as the nucleus and the cell membrane, but also of individual chemical compounds in the cell..." (17)

branes of a more primitive but similar form, existed before life did, and actually provided the morphological basis for the development of the cell. If this is the case, then the similarity of biological membranes is no great wonder - they were on the earth before cell metabolism, genes, and biological evolution existed! If some primitive membrane was a motive force in biogenesis itself, then perhaps cell function can be appreciated in terms of membrane structure, as well as vice-versa.

REDEFINITION OF THE CELL

While the biological membrane is defined without too much difficulty*, the condition of the presence of the cell membrane is usually used in defining the cell itself.**

This leads us to the following semantic problem: if one of the conditions for the definition of a cell is the membrane, the cell could not have preceded the membrane. We must therefore extend our definition to include those bodies which may have existed at one time, which were capable of the same or similar metabolic and reproductive properties as the primitive unicellular organisms we recognize today, but were either devoid of a separate phase membrane, or possessed a membrane of structure and composition removed from the biomembrane we recognize today.

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* "Biological membranes are continuous structures separating two aqueous phases. They are relatively impermeable to water - insoluble compounds, show a characteristic trilaminar appearance when fixed sections are examined by electron microscopy, and contain significant amounts of lipids and proteins." (19)

** "Basic to the definition of a cell is a membrane separating the activities within from the surrounding environment" (20)

THE CELL CAME FIRST

A number of theories exist concerning the evolution of living systems from inorganic beginnings (21-24). The most plausible hypothesis involves the synthesis of organic molecules in a reducing atmosphere, their dissolution into the primeval oceans, followed by subsequent polymerization and organization, culminating in a separate primitive biological system, without genes but with a basic metabolism and the ability to grow and reproduce.

At first sight, the most difficult part of this prebiological evolution to visualize is the separation of part of this primeval ocean into a separate physical system; in other words, the ~~mmp~~ morphogenesis of the cell. However, at least three types of relevant systems have been investigated. The first two, coacervates (~~24~~21,25), and protenoid microspheres (22), are microscopic drops of polymers which can form spontaneously in aqueous solution. The most striking features of these systems are abilities of growth and division, of absorbing materials against concentration gradients, and of certain catalytic reactions, provided that the enzyme is one of the polymers present.

These systems are very enlightening and show relatively simple examples of aqueous solutions in which organic and biological molecules can separate out into a separate phase with distinct morphological characteristics. What neither system does exhibit, however, is a membrane ~~mf~~ which constitutes a separate phase and of unique composition, as we find in present-day cells. In the coacervates, the interface with the aqueous medium is capable of selective permeability. The protenoid microspheres show ~~i~~ osmotic sensitivity, and, upon electron microscopic examination, exhibit what looks like a membrane. The pro-

tenoid microspheres, however, neither contain nor incorporate lipids.

Although these models simulate many facets of life and primitive organisms,, they are not possessed of a biological membrane nor a reasonable facsimile thereof. To assume that such a system evolved into a living cell, one would have to postulate the arrival of the membrane at a later date. Even if we ~~are~~ accept the adsorption of a biological membrane to a cell whcih is already metabolizing and reproducing, it is still hard to reconcile present-day cells with these drops of gelled polymers: cytoplasm is patently water-soluble.

THE MEMBRANE CAME FIRST

Since the bulk of work with the systems just mentioned, the ubiquity of the cell membrane has been recognized. It would seem that spontaneous systems involving membranes similar to biological ones should be more credible.

The experimental basis for such artificial membrane systems in aqueous solution is firmly established, using both molecules extracted from biological membranes (such as phospholipid mixtures and extracts (26)), simpler molecules (such as long-chain alcohols and fatty-acids (27)), whose synthesis under primitive conditions is plausible (28), and combinations of lipids and specific membranal proteins (29).

These molecules are all of an amphipathic nature (they contain both polar and non-polar groups). Upon addition to water, these immiscible molecules form layers on the surface of the liquid, but upon mechanical shaking disappear into solution. Microscopic examination reveals that the molecules form thermodynamically stable aggregates. Among these aggregates, vesicles, consisting of a thin membrane enclosing a small volume of solution, are found (29). Isolated membranes show similar behaviour (30).

Many similarities in structure and physical properties exist between biological membranes and artificial ones created with a variety of amphipathic molecules (28, 31).

Goldacre (18) postulated that such vesicles could have been the morphological basis of cell development. These vesicles could have been created within the primeval organic sea by a variety of mechanical disturbances (such as wind and waves The very creation of these vesicles separated the internal solution from the external by a semi-permeable membrane (30). Different molecular species and solute concentrations could have evolved within these membrane-bound bodies. Eventually some sort of primitive metabolism may have arisen, involving relatively simple catalytic agents, and perhaps utilizing the

membrane surface itself as a template (28) or catalyst* (32). ← simple peptides i.e. vesicles

The membrane hypothesis is ~~a~~ credible for three reasons. Firstly, the formation of these vesicles is spontaneous and thermodynamically favourable. Secondly, many similarities exist between ~~artificial~~ artificial membranes composed of a variety of of molecules, and biological membranes. Finally, the system does not require the synthesis of complicated molecules whose presence in the postulated primeval "organic soup" is unreasonable.

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* N.K. Adam writes,"The chance of reaching a reactive state in two molecules simultaneously increases with the square of time during which they are in contact, so that the function of the surface is to hold them close together for a time sufficient to 'make up their minds'." (32)

DISCUSSION

Need there be a membrane?

According to the proponents of the development of protenoid microspheres, coacervates, and related polymeric microbodies, the biological membrane is unimportant. Their systems have a primitive compartmentation, a primitive metabolism, ability in some cases to burst or bud and thus form progeny, and selective absorption of external solutes. These systems do not require a lipid-based membrane. The question which immediately arises is why do all cells have such membranes? If the primitive cells could do so well without a membrane, why did they later employ one? Why can we not find today any example of a cell, however primitive, without a lipid-based cell membrane? Lipids are neither adsorbed nor incorporated in the polymeric systems. Does this mean that the membrane arose much later in chemical evolution, under control of an early genetic system? Did the membrane evolve in different cells at different times? While none of these suggestions can be refuted, it remains to be demonstrated why a cell already viable, with an insoluble cytosol should develop a membrane which separates two aqueous solutions.

Problems of Cell Development Within a Primitive Membrane.

Provided that the cell evolved within a closed membrane of amphipathic molecules, a number of questions can be raised. Given that primitive membrane vesicles existed long before the development of the genetic apparatus, what connection can there be between primitive membranes, composed of a heterogeneous array of randomly syn-

thesized molecules, and present biological membranes? Today, most cells synthesize their own major membranal components. These molecules are specific, and are incorporated in determined ratios into each membrane. Could the primitive gene have any way of knowing what kind of membrane was surrounding him, and code for the synthesis of the same molecules in the same ratio? Probably not. On the other hand, the gene may have coded similar molecules, which were of an amphipathic nature, and thus were initially absorbed into a membrane of exogeneous origin, and over a number of generations slowly diluted the non-genetic membrane components. In this case the composition of the membrane may have been radically altered, but the molecular structure would have had to remain essentially the same throughout the transition.

Support for this hypothesis comes from the Mycoplasma group of microorganisms which are adept at performing the opposite phenomenon. These simple cells can incorporate a variety of extraneous fatty acids directly from the medium into their membranes (33). Thus the membrane composition can be radically altered. While some physical characteristics, such as temperature dependent phase changes, undergo slight deviations, neither the structure of the membrane nor the viability of the microorganism is grossly affected.

lipids, indicative of a different type of membrane (36,37). Indeed, one of the main differences between procaryotic and eucaryotic cells is the absence in the former of organelles bounded by a lipid-protein membrane.

The inability of de novo synthesis in the cell is widespread. Bacteria are incapable of de novo synthesis of cell wall. Genes, RNA and protein must be synthesized from their respective templates. De novo synthesis, however does exist. A motile bacteria with a single polar flagellum divides, giving rise to two sister cells, one of which must synthesize a new flagellum where none previously existed.

Biological evidence indicates that although the membrane is vital, the genetic control over it is limited. It is true that in the normal case specific membrane proteins are coded for, and specific enzyme pathways synthesize the lipids. These two major components are then incorporated in a sometimes dependent (38), sometimes independent (39), more-or-less regulated manner into a particular membrane. While the mechanism of incorporation itself is poorly understood, it is clear that the units which undergo incorporation cannot undergo self-assembly as the subunits of the flagellum do. As well, leeway exists in the composition of the membrane both in the lipid (33) and in the protein (38) entities. All cells encounter problems in synthesizing new membranes with a lipid-protein composition. Procaryotic cells do not do so, and eucaryotes have developed complicated organelles to this end. These observations strengthen the hypothesis that the membrane existed in the primitive cell before the genetic apparatus developed, and that in the present state of biological systems the membrane still has at least a modicum of the independence from cellular control that it once possibly had in the primeval sea.

The Uniqueness of the Biological Membrane.

Perhaps the general structure of the biological membrane is not the optimal one, but rather one the cell cannot rid itself of. Certainly, a great variety of semi-permeable membranes exist, of varied composition, and structure.(40) While it is usually taken for granted that a lipid-based membrane was arrived at after a lengthy evolutionary development, it is plausible that the cell has been engaged, instead, in correcting the inadequacies of a membrane structure which it is unable to change. If the membrane came first, then the cell developed within a membrane whose structure was determined by physical, not evolutionary laws. To undergo transition to another membrane structure, the cell would be forced, at some stage, to disrupt its existing one. And this would cause death. So, instead, the genetic apparatus has compensated for the inherent ineptitudes in the primitive membrane, composed of random amphipathic molecules, by coding for the incorporation of specific molecules to fulfil functions not possessed intrinsically by a random membrane, such as amino-acid transport and energy conversion (30).

Thus we see that the universal structure of the membrane may have more of a historical than functional nature.

Cell Structure and Function.

In recent years it has become evident that the approach of reconciling structure on the cellular level solely in terms of discernible function is incomplete. There exists good evidence for the hypothesis that the origin of a number of subcellular bodies is not due to their evolutionary development within the cell, but rather to a primitive symbiosis, which benefited development. These organelles are postulated to have once been bacteria which took up what turned out to be permanent residence within the host cell. The evidence for this hypothesis has been most strongly demonstrated for the mitochondria (41).

A similar logic can perhaps be applied as well, to biological membranes. Arguments have been provided which indicate that the membrane may have existed before the first cell. While it is evident that the membrane has evolved in different directions in different cells and within the cell itself in eucaryotes, it may be just as correct to postulate that the general structure of biological cells themselves, is in part an adaptation to the properties of the membrane.

Cell Structure in Terms of the Membrane.

A number of cell characteristics can be examined in terms of the shortcomings of the membrane. For example, it can be argued that the osmotic sensitivity of lipid-protein membranes forced cells which live under conditions in media of varying tonicity (such as bacteria and plants) to develop cell walls, at considerable expense of substrates, and chemical energy and enzyme synthesis. If the membrane were not so fragile, this would not be necessary.

Another example is water content. Bacteria contain up to 90% water under conditions of growth. Why this great preponderance of water? Water, it can be argued, is the universal solvent. Organic chemists know that reactions in solvent occur much faster than the mixing of two reactive powders. On the other hand, why should rate be a crucial factor in biological development? If the development of life itself took over a billion years, what difference should the rate of metabolism have on the organization of a particular organism? However, it could be that during the development of primitive cells, assuming the membrane hypothesis, that the vesicles in the primeval ocean had no control over the water level. While the semi-permeable lipid and random amphipathic molecule membranes are not ordinarily permeable to most chemical species, they are freely permeable to water.(42) These first organisms, then were prey to osmotic and chemical potential. The intracellular water concentration was determined by the Donnan equilibrium (43). The primitive cells which developed inside these vesicles may have had no alternative but to build their structure and metabolism in dilute aqueous medium. Thus it has remained. This high water level must still be maintained today in organisms which live outside of water. Thus, the observation that cells require a high concentration of water in order for normal metabolism, may in part be due to historical necessity and subsequent adaptation, rather than an evolutionary search for the optimal water concentration.

The theories on the morphological development of primitive cells in the primeval sea can be divided into two categories: those in which a thin membrane composed of amphipathic molecules plays a central role, and those in which the membrane is ignored and does not play a role.

Since membranes are so vital a part of biological machinery, it is difficult to conceive that they were adsorbed onto an already metabolizing and reproducing cell.

The observation that some membranes may be supplemented with extraneous lipids, and that cells are incapable of de novo membrane synthesis indicates that a certain gulf exists between the membrane and the genes. These points support the hypothesis that the morphological basis of the cell lies in aqueous membrane-bound vesicles with the same general structure as present day cell membranes, probably of a simpler molecular composition.

If the membrane came first, the following corollary is suggested: when an attempt is made to explain the ubiquity of the biological membrane, both the metabolic function and the possible evolutionary significance should be considered.

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